Seminars in
Infectious
Disease

Perinatal and
Neonatal Infections

JOSEPH W. ST. GEME, JR., MD, *Torrance, California*

TWO IMPORTANT DEFINITIONS should be made
before discussing the more common acquired bac-
terial and viral infections of very early infancy.
Perinatal infections may be characterized by their
appearance within the first few days after birth
or the first two weeks of life. Although perhaps
an arbitrary exercise in semantics, *neonatal* infec-
tions may be defined as infections which occur
later, between three and six weeks of age. This
paper will discuss the significance of the separa-
tion of infections of very early infancy into these
two categories and the importance of this separa-
tion from a conceptual viewpoint. Infections,
which (by strict definition of the word congenital)
are acquired transplacentally during embryonic
and fetal life, will not be discussed.

Clinical Manifestations

The clinical signs of perinatal and neonatal in-
fections are similar and uniquely vague, particu-
larly if the later infection occurs in a premature
infant. The physiologic fragility of thermal regula-
tion in the newborn, most notably premature in-
fants, conditions the occasional appearance of
hypothermia—rather than fever—with sepsis.
Unexplained apnea may be the only signal of in-
fection, as was witnessed in two recent outbreaks
of nosocomial neonatal echovirus infection which
occurred in infant special care units.[1,2] The cere-

From the Department of Pediatrics, Harbor General Hospital,
Torrance, and University of California, Los Angeles, School of
Medicine.
Submitted, revised, August 30, 1974.
Reprint requests to: J. W. St. Geme, Jr., MD, Department of
Pediatrics, Harbor General Hospital, UCLA School of Medicine,
1000 West Carson Street, Torrance, CA 90509.

bropathic element of perinatal and neonatal in-
fections may be discerned by subtle motor lapses
rather than overt tonic-clonic convulsive episodes.
Idiopathic hyperbilirubinemia of the indirect un-
conjugated type may indicate early perinatal in-
fection, and because of concomitant cholestatic
hepatitis late neonatal infection, particularly of
the urinary tract, may be associated with elevation
of direct-reacting conjugated bilirubin in the
serum.[3,4] Early infections seem to impair hepato-
cytic conjugating functions, while late infections
disrupt canalicular secretory processes and may
be confused with biliary atresia or neonatal hepa-
titis. It is difficult to emphasize adequately the
subtlety of failure-to-thrive in a septic infant, the
importance of detecting this early sign of abnor-
mality and the incalculable value of experienced
nursing personnel who are ordinarily the first to
sense minor alterations of infant behavior (for
instance, poor suck, more voluminous regurgita-
tion, respiratory irregularity, looser stools, tran-
sient cyanosis and hypoactivity). Physical findings
of bacteremia are few, and even during late infec-
tion—when meningitis may also accompany sys-
temic infection—one may not be able to elicit
signs of meningeal irritation.

Incidence

Infection occurs in two peaks, the early peri-
natal infection and the late neonatal infection, as
defined above. The overall incidence of sepsis
during early infancy ranges from 1 in 500 to 1 in
1,600 live births.[5,6] In our experience[7] the num-
ber of perinatal infections is almost twice that of

neonatal infection and the analysis of bacterial meningitis in the Collaborative Perinatal Research Study supports this observation.[6]

The risk of developing significant perinatal bacterial infection is increased ten times if prolonged rupture of amnionic membranes (beyond 12 to 24 hours) has occurred, and increased 100 times if febrile amnionitis has complicated prolonged membrane rupture.[8] In the event of prolonged membrane rupture and the intensified danger of maternal amnionitis, identification of the pathogen and the infant at risk may be pursued by culture of the vagina and cord blood, and of the gastric contents, axilla and umbilicus of the suspect infant. Hosmer and Sprunt[9] have pointed out the problems of getting significant clinical and microbial data by these techniques and stress the importance of duplicate blood cultures of the infant from different sites. If the same organism is recovered from most of these culture sites, certainly from blood, a presumptive diagnosis of high risk latent infection might be made and precise antimicrobial therapy begun.

Scanlon[10] has recently reported that with a Gram smear of the auditory canal, a truly infected infant—born of a mother with ruptured and possibly infected membranes—may be identified simply by searching for three or more polymorphonuclear leukocytes per high power field. A lumbar puncture should be included when considering infection in a very young infant, since in 30 to 50 percent of these infants meningitis is present or meningitis in addition to bacteremia.[5] When the puerperium is complicated by prolonged membrane disruption and maternal amnionitis, an infant should also be evaluated with lumbar puncture—particularly those infants with minimal symptoms, and perhaps even those without symptoms because the risk of their acquisition of infection may be as high as 10 percent.[8]

In approximately 1 percent of newborn infants, cytomegalovirus is excreted in urine.[11] This astonishingly high incidence of infection seems to be related to the shedding of this virus in the cervical secretions of 10 to 20 percent of women during the final trimester of pregnancy.[12-14] The greater incidence of cervical shedding of cytomegalovirus during the later stages of gestation may reflect the cumulative effect of pregnancy on reactivation of virus replication from latent sites of repose in genital tissues. In about 1 to 5 percent of nonpregnant women, cytomegalovirus is shed from the cervix.[15] Fortunately, this rather common peri-

natal virus infection is usually subclinical and associated with a generally favorable outcome during the ensuing years of childhood.[16,17]

Perinatal herpes simplex virus infection is estimated to occur in one of 7,000 births.[18] Since the type 2 genital strain of herpes simplex virus, which is the predominant species in these early perinatal infections, may be transmitted by the venereal mode, the incidence of this serious illness has probably risen over the past few years. As is true for maternal cytomegalovirus infections, herpes simplex virus type 2 can be isolated from the genital lesions and secretions of less than 1 percent of nongravid women but rises to a shed rate of 1 to 3 percent in pregnant women at term.[19] The speculation that pregnancy alters the relationship between the latent state and reactivation of virus is an attractive consideration for this virus also.

Approximately 70 percent of newborn infants with herpes simplex virus infection die, and the prognosis for normal cerebral function of survivors is poor. Effective antiviral drugs may ultimately modify these discouraging facts. On the other hand, specific antibiotic therapy has reduced the once awesome mortality of perinatal and neonatal bacterial infection from 90 percent to between 13 and 45 percent.[5] Unfortunately, the morbidity of bacterial infection persists and circumscribes varied neurologic problems, primarily seizures, hydrocephalus, mental retardation and learning disorders. The frequency of these overt and subtle neurologic sequelae reflects the species of bacterial pathogen and may be as high as 90 percent following Gram-negative bacterial infection and 50 percent following Gram-positive infection.[20]

Cause of Infection

Perinatal infections arise from contact with potential pathogens in the cervicovaginal canal. This may be illustrated by the striking occurrence of the initial cutaneous lesion of herpes simplex virus infection on the vertex of the scalp in many of the infants we have seen. It is as if a natural vaccination occurred as the presenting part was compressed by the cervical os and then the vaginal vault during the first and second stage of labor. Unfortunately, the virus involved is not an attenuated strain. Although it is difficult to prove, on rare occasions perinatal bacterial and viral infections may result from transcervical and transam-

nionic spread of pathogens despite the integrity of amnionic membranes.

Neonatal infections arise from the environment of care—most notably from isolettes, respirators, umbilical catheters, other infants and occasionally hospital personnel. All of these environmental elements are intensified if a major surgical procedure is carried out in a young infant. Fifty percent of umbilical arterial and venous catheter tips left *in situ* for several days yield bacteria, largely staphylococcal and pseudomonas organisms, when they are withdrawn and cultured.[21,22] About 10 percent of infants whose umbilical catheters have become pyogenic foci fail to clear the bacteria and develop significant bacteremia. A further alarming example of nosocomial infectious problems within neonatal intensive care units has been the recent observation of serious outbreaks of infection with kanamycin-resistant Klebsiella species.[23-25] The reservoir of infection in these outbreaks has been the infants themselves and nursing personnel have played an enhancing role by presumed and occasionally verified manual transmission of the pathogen.

The neonatal intensive care unit is a particularly provocative setting for the evolution of later neonatal bacterial infections. A varied assortment of infants with serious medical and surgical problems reside in these units for extended periods of time. There is widespread use of isolettes, respirators and vascular catheterization for monitoring and therapeutic purposes. The uniform and usually appropriate use of antibiotics within special care units represents a potentially powerful force for selection of resistant pathogens. The recent outbreaks of antibiotic-resistant Gram-negative bacillary infection are not surprising. In addition to the vigorous and continued cleansing of isolettes and the tubing and nebulizing components of respirators, and the substitution of peripheral needles for central catheters in the implementation of fluid and metabolic therapy, it may become necessary to restrict antimicrobial therapy more rigidly only to those infants in whom there is documented bacterial infection. Since the patterns of admission to intensive care units ordinarily preclude strict adherence to a cohort system of infant location within the unit, the cohort deployment of nursing personnel may prove to be a necessary adjustment to prevent and contain serious nosocomial infection.

An interesting example of nosocomial neonatal bacterial illness where nursing personnel may have played a major role is the emergence of exfoliative toxin-producing Staphylococcus aureus infection.[26] The phage type 71 straphylococcal infection produces Ritter's disease and occurs as a late neonatal infection. The organism is acquired in regular full-term nursery units during the short time span of modern newborn care, apparently from nursing personnel with nasal colonization by this pathogen. The epidemiology and ecology of this new neonatal staphylococcal pathogen is similar to that of the phage type 80/81 of the late 1950's.[27]

Perinatal Pathogens

Infections occurring during the first few days to two weeks after birth evolve from contact with potential pathogens in the cervicovaginal flora. These bacteria, fungi and viruses are of maternal origin and include Escherichia coli, group B beta hemolytic streptococci, gonococci, Treponema pallidum, Listeria monocytogenes, Bacteroides species, Candida albicans, cytomegalovirus and herpes simplex virus type 2. Prolonged rupture of the amnionic membranes before birth intensifies the risk of infant infection. The increase in sexual promiscuity during the past decade has also increased the incidence of perinatal infection. In addition to gonococcal and luetic infection, venereal transmission has been shown to exist for cytomegalovirus and the type 2 genital strain of herpes simplex virus.[28,29] As has been suggested, prolonged gestation permits the nurturing of microbial replication and the reactivation of some viruses.

The onset of perinatal infection, either very soon after birth or seven to 14 days later, may reflect the effect of differing inocula of these cervicovaginal pathogens on the incubation period of septic illness in infants.

An intriguing change in the pattern of pathogens has occurred during the past 20 years. The group B beta hemolytic streptococcus, a well recognized vaginal streptococcus and a rare cause of sepsis in the newborn in the past, has become a predominant pathogen in neonatal units throughout the country.[30] The incidence of group B beta hemolytic streptococcal shedding in the vagina may be as high as 30 percent in pregnant women.[31] The usual carrier rate for this organism in pregnant and nonpregnant women is approximately 5 to 10 percent, although Franciosi and colleagues[32] have suggested that the possibly more virulent

group B streptococcal types Ia, Ib and Ic may be substituted during late gestation for the ordinarily prevalent type III.

Neonatal Pathogens

The organisms producing these late infections, between three and six weeks after birth, arise primarily from the environment of care within the hospital or the home, although some of these infections are caused by lingering pathogens of earlier maternal origin. In our own experience only a third of all infections during the first two months of life occur during this later three to six week period. The prominent pathogens include Klebsiella, Aerobacter and Proteus species; Staphylococcus aureus; phage type 80/81 and 71; meningococci; Hemophilus influenzae; Pseudomonas aeruginosa; Candida albicans; group B coxsackieviruses; echoviruses; influenza virus; parainfluenza viruses and respiratory syncytial virus.

The occasional meningococcal and Hemophilus influenzae infections reflect the absence of transplacental maternal antibody in the sera of these young infants. The increasing incidence of Hemophilus influenzae infection emphasizes the changing pattern of immunity in adults. In the 1930's, 90 percent of cord blood contained Hemophilus influenzae bactericidal antibody, but in the 1970's only 10 percent of cord blood contained antibody.[33] Analysis of peripheral blood samples from mothers has revealed that only 25 percent contain bactericidal antibody.[33] Widespread antibiotic therapy has apparently diminished the natural immunity of adults acquired by repeated unchecked Hemophilus influenzae infections during the preantibiotic era.

Pseudomonas infections are rare, fortunately, as continued surveillance and eradication of the nosocomial sources of this important water-bug in isolettes, respirators and handwashing facilities has curbed significant outbreaks within neonatal units. Water bugs were an important and serious cause of epidemic, nosocomial neonatal infection in the early 1960's, with widespread contamination of standard equipment and plumbing components of routine full-term and preterm infant care units.[34-37] The rapid attack on this problem with simple adaptation of improved housekeeping techniques, better sanitation and more fastidious decontamination of equipment proved successful and timely, since neonatal intensive care units were just beginning to develop.[38]

Candidal neonatal infections are on the rise as a result of increasing implementation of parenteral hyperalimentation with central venous catheters.[39] We have seen several infants with widespread visceral and embolic candidemic disease, all of whom have responded satisfactorily to vigorous amphotericin therapy.[40] Clearly, these candidal neonatal infections evolve as the cutaneous barriers and natural resistance of the infant host are altered. These fungi arise from the infant or the immediate environment, although maternal vaginal candidal organisms usually seed the gastrointestinal tract of infants at birth.

We seldom witness the form of perinatal group B coxsackievirus infection which was described in the earlier literature, heralded by maternal symptoms at the time of parturition with subsequent fulminant illness in the infant.[41] Frequently, infants are admitted to special care units with the onset of late neonatal coxsackievirus or echovirus infection, characterized by unexplained fever or overt aseptic meningitis. These viral infections are usually benign, particularly in full-term infants, and often misdiagnosed as obscure or partially treated bacterial meningitis.[42] If these infections are examined by careful virologic techniques, we suspect that they will comprise a substantial component of late neonatal infection during the summer and fall months. These viruses may spread within special infant care units as nosocomial infections and although the afflicted host is often a preterm infant the outcome is rarely fatal.[1,2,43,44]

Outbreaks of febrile acute respiratory illness have occurred in preterm infant units caused by adenoviruses,[45] echoviruses,[46] parainfluenza viruses,[47] and respiratory syncytial virus.[48] The dissemination of these respiratory virus infections within preterm infant units may be far reaching, since these infants are kept in these units for prolonged periods and the incubation-transmission interval from one infant to another may be a relatively brief three to seven days. Recently, an outbreak of influenza was observed in a newborn nursery in Montreal, one of the few outbreaks from this cause ever described.[49]

A unique, late neonatal Escherichia coli infection is the syndrome of bacteremia, pyelonephritis, cholestatic hepatitis and direct hyperbilirubinemia.[3,4] As mentioned before, this illness may be confused with biliary atresia or neonatal hepatitis. Perinatal Escherichia coli sepsis during the early days of life may produce indirect hyperbilirubinemia.

Group B streptococcal infection may also ap-

pear as a late neonatal infection.[30,32,50,51] These streptococci may represent persisting maternal organisms acquired at birth, or possibly pathogens newly acquired from colonized infant cohorts.[31]

Factors of Host Resistance

In our experience, a third of the cases of perinatal and neonatal septicemia occur in preterm infants.[7] This is a uniform observation throughout the country and must be considered in the light of the fact that only 10 percent of all births are preterm.[5,6] An explanation for this discrepancy may be derived in part by examination of the various facets of innate and adaptive resistance to bacterial, fungal and viral infection. Although there is some disagreement,[52,53] the polymorphonuclear leukocyte of the preterm infant is intrinsically capable of undertaking normal phagocytosis and intracellular bacterial killing. Lower levels of antibody and complement in the serum of preterm infants account for impaired leukocytic function in vitro when the leukocyte and serum of preterm infants are tested together.[54-57] Defects do exist in the chemotactic responses of newborn leukocytes.[58] So, there is a problem with the important inflammatory response, but it is not known whether there is a difference in this regard between preterm and full-term infants. Lymphocyte or T-cell mediated cellular immunity, particularly important in the control of fungal and viral infections, is no more diminished in preterm than full-term infants.[59-61] Levels of serum immunoglobulin G (IgG) and immunoglobulin M (IgM) and opsonizing and neutralizing antibody of maternal transplacental origin, are somewhat lower in the preterm infant.[55,57,62,63] However, the ability of the low birth weight host to develop antibody is sufficient and comparable to the full-term infant.[64-66] Dealing with bacterial infection, IgG opsonins participate in the phagocytic killing of Gram-positive organisms, while IgM antibodies in concert with complement destroy Gram-negative organisms by lysis. IgM and, to a lesser extent, IgG antibodies also opsonize Gram-negative bacilli for phagocytosis. As has been pointed out, complement levels are lower in the preterm infant, and complement seems to play the major role not only in bacterial lysis and opsonization but also polymorphonuclear leukocytic chemotaxis.[57,58,67] Immature and preterm erythrocytes contain lower levels of 2, 3-diphosphoglycerate and are consequently less able to release oxygen to tis-

sues.[68] Oxygen is vitally important in the key metabolic steps prerequisite to successful intraleukocytic kill of bacteria in infected tissues.[69]

The poorly understood blood-brain barrier is suspect in preterm infants and may be an important factor in the development of meningitis with perinatal and neonatal bacteremia, intensifying the seriousness of the sequelae of these infections during early infancy.

Ecologic, environmental and nosocomial phenomena may be considered strange bedfellows for a discussion of host resistance to infection in preterm infants. However, preterm infants are the most frequent recipients of umbilical catheters, are most frequently exposed to the respiratory and the toxic effect of oxygen on intrapulmonary phagocytic and ciliary function, are most frequently produced by pregnancies complicated by prolonged rupture of membranes and are kept in a hospital milieu—often an intensive care milieu —for the longest periods of time. Preterm infants are also the most frequent subjects of significant surgical procedures, attended by prolonged antibiotic manipulation of microbial flora, intensive violation of integument by parenteral therapeutic ventures and drainage of cavitary operative sites.

Therapy

With the recent emergence of group B beta hemolytic streptococcal perinatal and neonatal infection, some clinics have substituted penicillin for ampicillin as the antimicrobial agent directed at Gram-postive pathogens.[70] Continued study of group B streptococcal infection throughout the country suggests that there is no significant difference in the therapeutic efficacy of either antibiotic.[50,71] Kanamycin has been the usual accompanying antibiotic in the management of perinatal and neonatal sepsis, targeted for the Gram-negative spectrum of the common pathogens.

Recently, there has been some unrest about kanamycin in some sections of the country because of the gradual emergence of kanamycin-resistant Escherichia coli during the past 10 years.[72] McCracken[72] has reported that 1 to 10 percent of blood culture isolates in his clinic were resistant to kanamycin from 1963 to 1967, whereas from 1970 to 1971, 30 percent of such isolates were resistant. A survey of seven other neonatal units throughout the country disclosed that 20 to 30 percent of Escherichia coli were resistant to kanamycin and ampicillin. Only 5 percent of Escherichia

coli were resistant to gentamicin and polymyxin B. However, other neonatal care centers report continued susceptibility of the majority of coliform and other Gram-negative pathogens to kanamycin.[73] The practical conclusion which may be derived from these observations is that personnel in each neonatal unit must continue to examine the antimicrobial susceptibility of the pathogens recovered from its patients.

We have been concerned about the diffusion of kanamycin into the cerebrospinal fluid.[74] Although the data of Eichenwald[75] document adequate levels of kanamycin in the spinal fluid of infants with meningitis, our pharmacologic studies indicated that its levels in spinal fluid may be inadequate to eradicate Gram-negative pathogens. The substitution of gentamicin for kanamycin must be conducted usually with intrathecal administration if one is dealing with meningitis, since the spinal fluid concentration of gentamicin is quite low following parenteral therapy. The same pharmacologic principle obtains if polymyxin B is used to treat resistant Gram-negative organisms.

Our usual therapeutic strategy for apparent perinatal and neonatal sepsis involves the use of ampicillin and kanamycin after the procurement of blood, urine and spinal fluid cultures. If the spinal fluid is grossly purulent, intrathecal gentamicin or polymyxin is administered at the time of the initial lumbar puncture. Also, if the spinal fluid is visibly infected at the outset, we repeat the lumbar puncture 24 hours after the initiation of antimicrobial treatment to determine whether the pathogens have been eradicated from the spinal fluid. We consider this maneuver an *in vivo* antibiotic sensitivity test. If pathogens persist in the spinal fluid we begin or continue intrathecal therapy, or modify antibiotic selection after identifying the pathogen and carrying out quantitative disc sensitivity tests.

McCracken[20] has recently summarized a revealing experience with bacterial meningitis in newborn and young infants. His observations in Dallas spanned 1966 to 1971 and included 38 infants, 21 percent of whom were preterm infants. The mortality rate was low, 19 percent, but the morbidity data were very provocative, relating quite clearly to the type of pathogen and the immediate therapeutic response. Antimicrobial treatment consisted of parenteral administration of ampicillin or penicillin combined with kanamycin or gentamicin. Almost a third of the patients were also treated with intrathecal or intraventricular

administration of polymyxin B, kanamycin or gentamicin. Gram-positive pathogens, largely group B streptococci, were promptly eradicated from the spinal fluid and 50 percent of the infants so treated were neurologically normal at 2 to 3 years of age. Gram-negative pathogens, primarily Escherichia coli and Klebsiella species, were very slowly cleared from the spinal fluid, the organisms persisting in the spinal fluid for as long as one week, and only 10 percent of these infants were free of neurologic sequelae at 2 to 3 years of age.

Other speculative but untested components of therapy include gamma globulin, a source of IgG opsonins, and fresh adult whole blood transfusion which provides more suitable levels of erythrocyte 2, 3-diphosphoglycerate plus IgM lytic opsonins and complement. Doppler techniques and intra-aortic direct measurement of blood pressure offer superior methods for the detection of shock in perinatal and neonatal infection. The supplementation of routine antibiotic therapy with the physiologic control of shock, acidosis and hypoglycemia may offer the ultimate solution for not only the residual mortality but also the intractable, serious neurologic morbidity. Colloid, isoproterenol and enormous vasoactive doses of hydrocortisone should be explored more vigorously for their contribution to the management of these serious infections. Sodium bicarbonate and parenteral administration of glucose are standard therapeutic modalities in infant special care units and must be considered in the management of infectious illness also.[76,77]

Disseminated intravascular coagulation occasionally complicates infection in young infants and intravenous heparin may offer helpful treatment—although the titration of anticoagulation may be delicate. The use of heparinized whole blood for other purposes as discussed above may also suffice to control moderate intravascular coagulopathy. Intravascular coagulopathy can be distinguished from the hemorrhagic disorder of profound hepatic dysfunction by the assay of factor VIII (AHG), which is decreased with intravascular coagulopathy and normal with liver disease.

Staphylococcal infection, more commonly now Ritter's disease produced by phage type 71 organisms, may be treated with uniform success with parenteral methicillin. As mentioned above, we have found amphotericin therapy of systemic candidal infection, including occasional intrathecal treatment, to be successful and free of therapeutic

complications.[40] We have gained some experience with parenteral and intrathecal treatment of systemic perinatal herpes simplex type 2 virus infection with cytosine arabinoside.[78] Infants have survived with and without such therapy and so we can draw no conclusion regarding the efficacy of systemic antiviral chemotherapy. Frankly, with a few exceptions, the experience throughout the country does not offer a great deal of optimism concerning chemotherapy of perinatal herpes simplex virus or cytomegalovirus infection with cytosine arabinoside, adenine arabinoside and 5-fluoro or 5-iodo-2-deoxyruidine.[79-84]

REFERENCES

1. McDonald LL, St Geme JW Jr, Arnold BH: Nosocomial infection with echovirus type 31 in a neonatal intensive care unit. Pediatrics 47:995-999, Jun 1971

2. Cramblett HG, Haynes RE, Azimi PH, et al: Nosocomial infection with echovirus type 11 in handicapped and premature infants. Pediatrics 51:603-607, Apr 1973

3. Bernstein J, Brown AK: Sepsis and jaundice in early infancy. Pediatrics 29:873-882, Jun 1962

4. Rooney JC, Hill DJ, Danks DM: Jaundice associated with bacterial infection in the newborn. Am J Dis Child 122:39-41, Jul 1971

5. Gotoff SP, Behrman RE: Neonatal septicemia. J Pediat 76:142-154, Jan 1970

6. Overall JC Jr: Neonatal bacterial meningitis. J Pediat 76:499-522, Apr 1970

7. Hemphill A, St Geme JW Jr, Anthony BF: Unpublished data

8. Good R, St Geme JW Jr: Unpublished data

9. Hosmer ME, Sprunt K: Screening method for identification of infected infant following premature rupture of maternal membranes. Pediatrics 49:283-285, Feb 1972

10. Scanlon J: The early detection of neonatal sepsis by examination of liquid obtained from the external ear canal. J Pediat 79:247-249, Aug 1971

11. Starr JG, Bart RD Jr, Gold E: Inapparent congenital cytomegalovirus infection. New Engl J Med 282:1075-1077, May 7, 1970

12. Numazaki T, Yano N, Morizuka T, et al: Primary infection with human cytomegalovirus: virus isolation from healthy infants and pregnant women. Am J Epidemiol 91:410-417, Apr 1970

13. Montgomery R, Youngblood L, Medearis DN Jr: Recovery of cytomegalovirus from the cervix in pregnancy. Pediatrics 49:524-531, Apr 1972

14. Reynolds DW, Stagno S, Hosty TS, et al: Maternal cytomegalovirus excretion and perinatal infection. N Engl J Med 289:1-5, Jul 5, 1973

15. Stagno S, Reynold DW, Smith R, et al: Cervical cytomegalovirus (CMV) excretion in pregnant and nonpregnant women: Suppression in early gestation. Program and Abstracts, 13th Annual ICAAC Meeting, Sep 19-21, 1973, Wash, DC

16. Kumar ML, Nankervis GA, Gold E: Inapparent congenital cytomegalovirus infection. A follow-up study. N Engl J Med 288:1370-1372, Jun 28, 1973

17. Melish ME, Hanshaw JB: Congenital cytomegalovirus infection. Am J Dis Child 126:190-198, Aug 1973

18. Nahmias AJ, Alford CA, Korones SB: Infection of the newborn with herpesvirus hominis. Adv Pediat 17:186-226, 1970

19. Nahmias AJ, Josey WE, Naib ZM, et al: Perinatal risk associated with maternal genital herpes simplex virus infection. Am J Obstet Gynec 110:825-837, Jul 1971

20. McCracken GH Jr: The rate of bacteriologic response to antimicrobial therapy in neonatal meningitis. Am J Dis Child 123:547-553, Jun 1972

21. Krauss AM, Albert RF, Kannan MM: Contamination of umbilical catheters in the newborn infant. J Pediat 77:965-969, Dec 1970

22. Balagtas RC, Bell CE, Edwards LD, et al: Risk of local and systemic infections associated with umbilical vein catheterization. Pediatrics 48:359-367, Sep 1971

23. Adler JL, Shulman JA, Terry PM, et al: Nosocomial colonization with kanamycin-resistant Klebsiella pneumoniae, types 2 and 11, in a premature nursery. J Pediat 77:376-385, Sep 1970

24. Hable KA, Matsen JM, Wheeler DJ, et al: Klebsiella type 33 septicemia in an infant intensive care unit. J Pediat 80:920-924, Jun 1972

25. Rosenblatt RM, Craig ME, Yoshimori RN, et al: Outbreak of type 60 Klebsiella in an intensive care nursery (ICN). Program and Abstracts, 13th Annual ICAAC Meeting, Sep 19-21, 1973, Wash, DC

26. Anthony BF, Giuliano DM, Oh W: Nursery outbreak of staphylococcal scalded skin syndrome. Am J Dis Child 124:41-46, Jul 1972

27. Nahmias AJ, Eickhoff TC: Staphylococcal infections in hospitals. N Engl J Med 265:74-81, 120-128, 177-182, Jul 13, 20, 27, 1961

28. Jordan MC, Rousseau WE, Noble GR, et al: Association of cervical cytomegaloviruses with venereal disease. N Engl J Med 288:932-934, May 3, 1973

29. Nahmias AJ, Dowdle WR, Naib AM, et al: Genital infection with type 2 herpes virus hominis. Br J Vener Dis 45:294-298, Dec 1969

30. McCracken GH Jr: Group B streptococci: The new challenge in neonatal infections. J Pediat 82:703-706, Apr 1973

31. Aber RC, Facklam R, Wilkinson H, et al: Nosocomial group B streptococcal infections in neonates. Program and Abstracts, 13th Annual ICAAC Meeting, Sep 19-21, 1973, Wash, DC

32. Franciosi RA, Knostman JD, Zimmerman RA: Group B streptococcal neonatal and infant infections. J Pediat 82:707-718, Apr 1973

33. Graber CD, Gershanik JJ, Levkoff AH, et al: Changing pattern of neonatal susceptibility to Hemophilus influenzae. J Pediat 78:948-950, Jun 1971

34. Sever JL: Possible role of humidifying equipment in spread of infections from newborn nursery. Pediatrics 24:50-53, Jul 1959

35. Wilson MG, Nelson RC, Phillips LH, et al: New source of pseudomonas aeruginosa in nursery. JAMA 175:1146-1148, Apr 1, 1961

36. Foley JF, Gravelle CR, Englehard WE, et al: Achromobacter septicemia—Fatalities in prematures. Am J Dis Child 101:279-288, Mar 1961

37. Becker AH: Infection due to proteus mirabilis in newborn nursery. Am J Dis Child 104:355-359, Oct 1962

38. Kresky B: Control of gram-negative bacilli in a hospital nursery. Am J Dis Child 107:363-369, Apr 1964

39. Curry CR, Quie PG: Fungal septicemia in patients receiving parenteral hyperalimentation. N Engl J Med 285:1221-1224, Nov 25, 1971

40. Klein JD, Yamauchi T, Horlick SP: Neonatal candidiasis, meningitis, and arthritis. J Pediat 81:31-34, Jul 1972

41. Fechner RE, Smith MG, Middlekamp JN: Coxsackie B virus infection of the newborn. Am J Path 42:493-505, Apr 1963

42. Nogen AG, Lepow ML: Enteroviral meningitis in very young infants. Pediatrics 40:617-626, Oct 1967

43. Eichenwald HF, Abubio A, Acky AM, et al: Epidemic diarrhea in premature and older infants caused by ECHO 18. JAMA 166:1563-1566, Mar 29, 1958

44. Berkovich S, Kibrick S: ECHO 11 outbreak in newborn infants and mothers. Pediatrics 33:534-540, Apr 1964

45. Eichenwald HF, Kotsevalov O: Immunologic responses of premature and full-term infants to infection with certain viruses. Pediatrics 25:829-839, May 1960

46. Berkovich S, Pangan J: Recoveries of virus from premature infants during outbreaks of respiratory disease—The relation of ECHO virus type 22 to disease of the upper and lower respiratory tract in the premature infant. Bull New York Acad Med 44:377-387, Apr 1968

47. Moscovici C, LaPlaca M, Amer J: Respiratory illness in prematures and children—Illness caused by parainfluenza type 3 virus. Am J Dis Child 102:91-95, Jul 1961

48. Berkovich S: Acute respiratory illness in the premature nursery associated with respiratory syncytial virus infections. Pediatrics 34:753-760, Dec 1964

49. Bauer CR, Elie K, Spence L, et al: Hong Kong influenza in a neonatal unit. JAMA 223:1233-1235, Mar 12, 1973

50. Barton LL, Feigin RD, Lins R: Group B beta hemolytic streptococcal meningitis in infants. J Pediat 82:719-723, Apr 1973

51. Baker CJ, Barrett FF, Gordon RC, et al: Suppurative meningitis due to streptococci of Lancefield group B: A study of 33 infants. J Pediat 82:724-729, Apr 1973

52. Miller ME: Phagocytosis in the newborn infant: Humoral and cellular factors. J Pediat 74:255-259, Feb 1969

53. Coen R, Grush O, Kauder E: Studies of bactericidal activity and metabolism of the leukocyte in full-term neonates. J Pediat 75:400-406, Sep 1969

54. Gluck L, Silverman WA: Phagocytosis in premature infants. Pediatrics 20:951-957, Dec 1957

55. Forman ML, Stiehm ER: Impaired opsonic activity but normal phagocytosis in low-birth-weight infants. N Engl J Med 281:926-931, Oct 23, 1969

56. Dossett JH, Williams RC Jr, Quie PG: Studies on interaction of bacteria, serum factors and polymorphonuclear leukocytes in mothers and newborns. Pediatrics 44:49-57, Jul 1969

57. McCracken GH Jr, Eichenwald HF: Leukocyte function and the development of opsonic and complement activity in the neonate. Am J Dis Child 121:120-126, Feb 1971

PERINATAL AND NEONATAL INFECTIONS

58. Miller ME: Chemotactic function in the human neonate: Humoral and cellular aspects. Pediat Res 5:487-492, Sep 1971

59. Gaisford W: The protection of infants against tuberculosis. Br Med J 2:1164-1171, Nov 12, 1955

60. Warwick WJ, Good RA, Smith RT: Failure of passive transfer of delayed hypersensitivity in the newborn human infant. J Lab Clin Med 56:139-147, Jul 1960

61. Uhr JW, Dancis J, Neumann CG: Delayed-type hypersensitivity in premature neonatal humans. Nature 187:1130-1131, Sep 24, 1960

62. Gitlin D, Rosen FS: Michael JG: Transient 19Sγ-globulin deficiency in the newborn infant, and its significance. Pediatrics 31:197-208, Feb 1963

63. Hyvarinen M, Zeltzer P, Oh W, et al: Influence of gestational age on serum levels of alpha-1-feto protein, IgG globulin, and albumin in newborn infants. J Pediat 82:430-437, Mar 1973

64. Uhr JW, Dancis J, Franklin EC, et al: The antibody response to bacteriophage φX174 in newborn premature infants. J Clin Invest 41:1509-1513, Jul 1962

65. Smith RT, Eitzman DV: The development of the immune response. Pediatrics 33:163-183, Feb 1964

66. Rothberg RM: Immunoglobulin and specific antibody synthesis during the first weeks of life of premature infants. J Pediat 75:391-399, Sep 1969

67. Fireman P, Zuckowski DA, Taylor PM: Development of human complement system. J Immunol 103:25-31, Jul 1969

68. Orzalesi MM, Hay WW: The regulation of oxygen affinity of fetal blood—I. In vitro experiments and results in normal infants. Pediatrics 48:857-864, Dec 1971

69. Babior BM, Kipnes RS, Curnutte JT: The production by leukocytes of superoxide, a potential bactericidal agent. J Clin Invest 52:741-744, Mar 1973

70. Whitworth TC, Sell SH: Beta-hemolytic streptococcus group B in neonates. Clin Res 20:106, Jan 1972

71. Baker CJ, Barrett FF, Gordon RC: Group B B-hemolytic streptococcal meningitis in infants. Clin Res 21:120, Jan 1973

72. McCracken GH Jr: Changing pattern of the antimicrobial susceptibilities of Escherichia coli in neonatal infections. J Pediat 78:942-947, Jun 1971

73. Reynolds D, Cassady G: Antibiotic resistance of E. coli isolates from neonates. Clin Res 20:104, Jan 1972

74. McDonald LL, St Geme JW Jr: Cerebrospinal fluid diffusion of kanamycin in newborn infants. Antimicrob Ag Chemother 2:41-45, Jan 1972

75. Eichenwald HF: Some observations on dosage and toxicity of kanamycin in premature and full-term infants. Ann NY Acad Sci 132:984-991, Jun 1966

76. Yeung CY: Hypoglycemia in neonatal sepsis. J Pediat 77:812-817, Nov 1970

77. Yeung CY, Lee VWY, Yeung CM: Glucose disappearance rate in neonatal infection. J Pediat 82:486-489, Mar 1973

78. Chow AW, Ronald A, Fiala M, et al: Cytosine arabinoside therapy for herpes simplex encephalitis—Clinical experience with six patients. Antimicrob Ag Chemother 3:412-417, Mar 1973

79. Feigin RD, Shackelford PG, DeVivo DC, et al: Floxuridine treatment of congenital cytomegalic inclusion disease. Pediatrics 48:318-323, Aug 1971

80. Kraybill EN, Sever JL, Avery GB, et al: Experimental use of cytosine arabinoside in congenital cytomegalovirus infection. J Pediat 80:485-487, Mar 1972

81. McCracken GH Jr, Luby JP: Cytosine arabinoside in the treatment of congenital cytomegalic inclusion disease. J Pediat 80:488-495, Mar 1972

82. Nolan DC, Lauter CB, Lerner AM: Idoxuridine in herpes simplex virus (type 1) encephalitis. Ann Intern Med 78:243-246, Feb 1973

83. Ch'ien LT, Cannon NJ, Charmaella LJ, et al: Effect of adenine arabinoside on severe herpesvirus hominis infections in man. J Infect Dis 128:658-663, Nov 173

84. Baublis JV, Buchanan R, Holland R: Diminished cytomegalovirus (CMV) excretion in congenitally infected infants treated with adenine arabinoside (Ara-A). J Pediat 83:156, Jul 1973